It appears likely, based upon all these data, that very high doses of estrogens may increase the risk, but that lower doses may not. Since currently low-dose estrogen-progestogen combined contraceptives are commonly used, any risk that might exist with the high dose may be nonexistent or minimal with the low doses. Table 14 gives some relative incidence of mortality for oral contraceptives taking Inman and Vessey's data as a high estimate example, and comparing this with postpartum state, auto accidents and cancer to help put the figures in perspective. Progestogen-only oral contraceptives have not been implicated with increased risk of vascular disease.[39-43] Although the case for cause and effect of thromboembolic phenomena is on shaky ground, it would appear unwise to use estrogen containing oral contraceptives in women with clear-cut predisposing factors for thromboembolism. Such factors would include congestive heart failure, significant edema from any cause, obesity, varicose veins, and history of thrombophlebitis or embolism. The history and controversy of the relation of oral contraceptives to thromboembolism is an excellent example to point out the great need for carefully controlled clinical experimentation.

Effects of Oral Contraceptives on Carbohydrate Metabolism

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THE INITIAL OBSERVATION of an impaired glucose tolerance in patients receiving oral contraceptives was made over ten years ago.[51] Since that time, this phenomenon has been examined in detail by many observers and has been reviewed several times,[52-54] most recently by Beck.[55] In the following discussion, we will examine this phenomenon in detail and attempt to answer three questions:

1. What are the impairments in glucose tolerance associated with ingestion of oral contraceptives?

2. Is the impairment of glucose tolerance the result of the estrogen, the progestogen or their combination?

3. By what mechanisms does this phenomenon occur?

The impairment of glucose tolerance is illustrated in Chart 10.[56] Two facts emerge: (1) The levels of fasting glucose are not significantly dif-

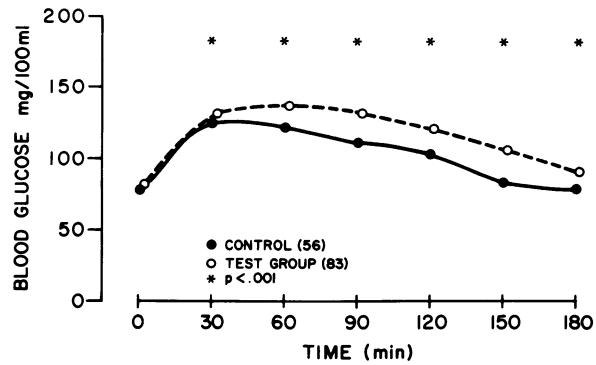

Chart 10.—Effect of oral contraceptives on glucose tolerance. This study adapted from Wynn and Doar[56] shows the impairment in glucose tolerance at all time intervals after the initial administration of glucose. Fasting levels of glucose, however, were normal. (Reproduced by permission from Wynn and Doar: Lancet 2: 715, 1966)

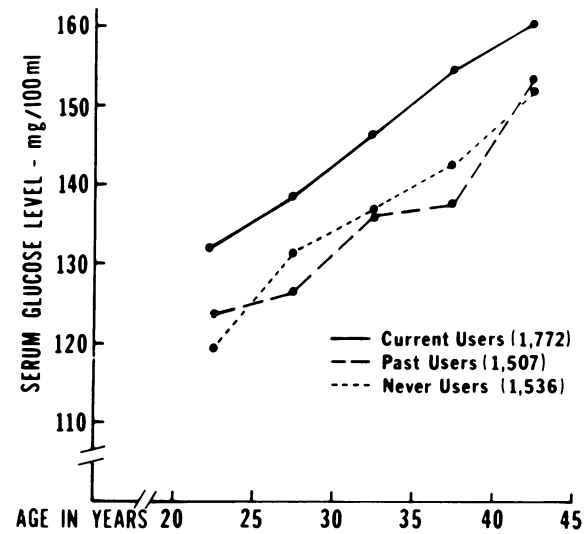

Chart 11.—Effect of age and oral contraceptives on glucose tolerance. The mean one-hour serum glucose concentrations after oral glucose, in current users, past users and non users of contraceptives steroids, is plotted against age. There was an increase in the levels of one-hour glucose value as a function of age. Women taking oral contraceptives had one-hour glucose values approximately 10 mg per 100 ml higher than the women who were not taking contraceptives or women who had previously taken them but had discontinued their use. (Reproduced by permission from Beck et al: Metabolism 22:846, 1973)

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ferent during treatment with oral contraceptives, and (2) glucose concentrations are elevated at all times after oral glucose. Since these early studies, it has become clear that the changes in glucose tolerance are in part related to the specific glucose tolerance. Fasting blood sugar may be normal[56-64] or elevated.[65,66] Whether or not the fasting glucose changes, however, there is a deterioration in oral glucose tolerance with most oral contraceptives and in most studies. The reported number of women whose glucose tolerance worsens, however, varies from one study to another. Of more importance is the fact that the impairment in glucose tolerance is reversible when the oral contraceptives are discontinued (Chart 11).[67] In this chart, the height of the one-hour glucose level after an oral glucose load is plotted as a function of age for women who are taking contraceptives, for women who have never taken contraceptives, and for a group of women who have discontinued taking them. This chart shows three things: (1) That there is an increase in the height of the one-hour glucose value in relation to age—that is, older women, whether on medication or not, have a higher level of glucose one hour after the oral administration of a glucose load than do younger women, (2) that after discontinuing the use of oral contraceptives, the one-hour glucose values return to normal, and (3) that the increase in glucose in women taking oral contraceptives is about 10 mg per 100 ml higher than in the other groups at all ages.

Elevated concentrations of insulin are commonly found in women taking oral contraceptives. This occurs in both the fasted state and during the oral glucose tolerance test. The higher fasting levels of glucose are thought to maintain fasting glucose at normal levels in most women. In addition to the consistent rise in insulin during therapy with oral contraceptives, there is a frequent,[60,61,66,68] although not uniform[62,64] increase in fasting growth hormone. In summary, then, oral contraceptives have a variable effect on fasting glucose which is frequently maintained within normal limits by the elevated fasting levels of insulin. During oral glucose tolerance tests, the rise in glucose and insulin are higher in women taking oral contraceptives than in controls. Fasting growth hormone levels may also be elevated.

Most oral contraceptives contain a combination of an estrogen and a progestational agent. Hence, the impairment in glucose tolerance could result from either agent alone or from their combination. To examine the role of the estrogenic component, Spellacy et al[69] performed intravenous glucose tolerance tests on a group of women before and six months after taking ethinyl estradiol, mestranol or Premarin® (conjugated estrogens, USP). Table 15 shows data for the sum of the glucose levels at 0, 1, 2 and 3 hours on women before and after six months of this treatment. No significant impairment in oral glucose tolerance was brought about by treatment with any of these estrogens for six months. These

TABLE 15—*Effect of Estrogenic Steroids on Glucose Tolerance**†*

Drug	*Number*	*Dose mg*	*Total Blood Glucose mg/100 ml*	
			Before	*After 6 Months*
Premarin®	42	1.25	411.9±14.6	431.1±15.6
Mestranol	60	0.08	445.1±17.0	429.3±15.7
Ethinyl estradiol	45	0.05	403.7±13.7	415.7±12.8

*Total glucose is the sum of the glucose values at 0, 1, 2 and 3 hours after an oral glucose load.
†Reprinted by permission from Spellacy: Am J Obstet Gynecol 114:378, 1972.

TABLE 16.—*Effect of Oral Contraceptives on Glucose Disappearance***

	Number Patients	*Duration (year)*	*K†*		*P§*
			Before	*During*	
Norethynodrel 5 mg + mestranol 0.075 mg	31	0.5	1.88±0.38‡	1.46±0.42	<.01
Megestrol acetate 5 mg + 27 mestranol 0.10 mg	27	1	2.05±0.60	1.94±0.55	NS¶
Megestrol acetate 4 mg + ethinyl estradiol 0.05 mg	15	1	2.62±0.32	2.52±0.31	NS
Chlormadinone acetate 0.5 mg	15	1	2.04±0.11	1.80±0.14	NS

*Adapted from Beck et al: Metabolism 22:846, 1973.
†K=the rate of fall of blood sugar in percent per minute.
‡Mean ± SEM.
§P=level of statistical significance.
¶NS=not significant.

data suggest that the estrogenic components of oral contraceptives are not alone responsible for the deterioration in glucose tolerance. One could also conclude from the data that the worsening of glucose metabolism was due to the progestational agent either alone or in combination with the estrogen. A similar conclusion is reached by comparison of the results of three studies with two estrogenic and two progestational compounds (Table 16).[57,64,70] The data in this table show a significant impairment in intravenous glucose tolerance when mestranol and norethynodrel were given as compared to mestranol or ethinylestradiol combined with megestrol, a different progestational agent. The importance of the progestational agent is also suggested in other studies. With progesterone alone,[70] there was no impairment in intravenous glucose tolerance. Of five patients who received norethindrone and mestranol, all had abnormal glucose tolerance test results.[71] When ethynodiol diacetate was the progestational agent, between 12 and 30 percent of the patients showed abnormalities in glucose tolerance.[63,65,72] Norethynodrel was also associated with impaired glucose tolerance.[73,74] Both of these progestational agents are derivatives of 19-nortestosterone. When chlormadinone acetate, a derivative of 17-αhydroxyprogesterone, was employed as the progestational agent, the percent of abnormal curve declined (Table 16).[75,76] These data, then, strongly suggest that it is the progestational agent which is principally involved in the impairment of glucose tolerance. In summary, it would appear that the impaired glucose tolerance and elevated level of insulin are primarily due to the progestational agent employed. The estrogenic component, however, may well have a synergistic effect. Oral contraceptives containing derivatives of nortestosterone appear to impair glucose tolerance more than those which are derivatives of progesterone.

The mechanism for these effects of oral contraceptives on glucose tolerance is unclear. One hypothesis has suggested that increased secretion of growth hormone may lead to the impaired glucose tolerance.[60,61,66,68] The possibility that growth hormone is involved was tested recently.[68] Normal and hypopituitary women were given an oral contraceptive containing mestranol and norethindrone. Tolbutamide was used to test the patients before and while receiving contraceptives. The anti-fertility drug blunted the fall in glucose and free fatty acids and enhanced the rise in growth hormone in the normal women. In the hypopituitary patients, oral contraceptives did not modify the response to tolbutamide. These differences resulting from the presence or absence of endogenous growth hormone lend support to the concept that growth hormone may be responsible for the impaired glucose tolerance. The studies of Spellacy et al[69] with estrogenic agents, however, do not support this concept. Both mestranol and ethinyl estradiol raise fasting growth hormone but are not associated with a deterioration in glucose tolerance. Thus, the mechanism for the impaired glucose tolerance seen with oral contraceptives still remains unclear.

Contraceptives and Lipid Metabolism

ROBERT H. FISER, MD*

DISORDERED LIPID METABOLISM is a troublesome and potentially serious side effect of contraceptive steroid therapy.[77-79] Although all lipid classes are affected by contraceptive use, elevations in plasma triglyceride and cholesterol concentrations have been the most consistent findings.[77-80] Increased levels of triglyceride and cholesterol have been used to explain the increased atherogenic index and the increased[81] incidence of myocardial infarction[82] and cerebral vascular accidents[83] in women using the pill compared with premenopausal women not using these steroids. Although there is no definite evidence on the causal relationship of disordered lipid metabolism to vascular disease with use of these drugs,[84] even this possibility makes it of clinical importance. Elevated triglyceride levels take on added significance with the recent report of Carlson and Böttiger 1972,[85] who found hypertriglyceridemia to be as great a risk factor for ischemic heart disease as hypercholesterolemia.

Increases in triglycerides and cholesterol concentrations are progressive, begin within a few weeks after beginning contraceptive therapy,[84] are dose-related[78,81,84] and plateau after several months. The elevated levels often persist after dis-

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